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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,741	12/20/2001	Shinichiro Kurosawa	OMRF:004US/SLH	9903

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	5

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/028,741	KUROSAWA ET AL.	
	Examiner	Art Unit	
	Claire M. Kaufman	1646	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-8, 17-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Esmon et al. (Thrombosis and Haemostasis (1999 August) 82(2):251-258) in light of Kurosawa et al. (#C8, Blood (1998) 91:725-727) and (#C7, J. Clin. Invest. (1997 July) 100(2) :411-418).

Esmon et al. teach a method of monitoring thrombin levels in patients undergoing anticoagulant therapy comprising the administration of hirudin, a specific thrombin inhibitor, by measuring circulating levels endothelial protein C receptor (EPCR), which receptors are necessarily soluble if circulating. Inhibition of thrombin by hirudin blocked increase in circulating EPCR (sentence bridging pages 254-255) in rats. Therefore, low levels of circulating EPCR corresponded to reduced levels of thrombin. Additionally, it was reported (p. 255, col. 2, third full sentence) that soluble EPCR was present at high levels in the plasma of normal individuals and was increased several fold in patients with diseases associated with hypercoagulation (autoimmune disorders and septic shock, specifically systemic lupus erythematosus (see #C8, Kurosawa et al., Fig. 1)). It is concluded that "This [monitoring of plasma EPCR levels] could prove useful in monitoring the progression of cardiovascular disease or the effectiveness of therapeutic interventions in these patients."

According to Kurosawa et al. (#C8), plasma EPCR levels were monitored by ELISA (*e.g.*, p. 726, middle of col. 1). This Kurosawa et al. reference is not necessary for anticipation of the claimed invention, but is provided only to confirm details referred to in the Esmon et al. reference.

Claims 17-30 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 5,804,392 (#A1).

US Patent 5,804,392 teaches a method of identifying individuals in a hypercoagulable state comprising measuring sEPCR, as well as identifying patients at risk of developing a hypercoagulability state comprising measuring sEPCR, wherein elevated sEPCR levels relate to hypercoagulability or an increased risk thereof. For example, plasma levels of sEPCR in patients with an autoimmune disease, sepsis correlated with abnormal coagulation were elevated (sentence bridging col. 3-4, col. 10, lines 57-59, EXAMPLES 3 and 4). Levels were assayed by ELISA immunoassay (paragraph bridging col. 12-13). Urine levels were also measured (EXAMPLE 2). Further, elevated levels of sEPCR were also said to be indicative of large vessel injury, which is accompanied by an increased risk of hypercoagulability (col. 10, lines 44-54).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 3 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Esmon et al. as applied to claims 1, 4-8, 17-30 above, and further in view of Hirsh et al. (#C6, Chest (1998 November) 114(5):445S-469S).

Esmon et al. is relied upon for the teachings above, but do not teach a method of monitoring the effectiveness of anticoagulation therapy, or measuring thrombin levels in patients undergoing anticoagulation therapy wherein the anticoagulant is other than hirudin or the therapy involves a vitamin K antagonist.

Hirsh et al. teach oral anticoagulant therapy with the anticoagulant Warfarin (*e.g.*, p. 446S, col. 1, second full sentence) and heparin (p. 463S, col. 2, second full paragraph). Also

taught is the use of a vitamin K antagonist in anticoagulant therapy (p.445S, col. 2, middle of first full paragraph). Hirsh et al. also teaches monitoring the effectiveness of anticoagulant therapy by measuring the prothrombin time (PT) as an international normalized ratio (INR, *e.g.*, Table 1 and section beginning at the bottom of p. 448S). Hirsh et al. points out that monitoring PT alone is not as reliable a measure of effectiveness of antithrombin therapy as the measure of both PT and INR (*e.g.*, p. 449S, col. 1, second to last paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to monitor the effectiveness of anticoagulant therapy by measuring circulating sEPCR using the method of Esmon et al., because Esmon et al. teach that circulating sEPCR levels are decreased by administration of the anticoagulant hirudin and increased in hypercoagulation states. Therefore the artisan of ordinary skill would have reasonably expected that the effectives of an anticoagulant, including heparin or Warfarin taught by Hirsh et al., could have been adequately monitored by measuring circulating sEPCR levels. Further, since Hirsh et al. discussed the difficulties in using PT and INR for monitoring anticoagulation therapy effectiveness, one of ordinary skill in the art would have desired to use a more consistent measurement and one that involved testing a single thing (sEPCR) instead of multiple interacting things (PT and INR). Further, because vitamin K antagonists were known to be anticoagulants, it would have been obvious to include a vitamin K antagonist when thrombin levels or anticoagulation therapy were being monitored.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Wu et al. (Chinese Journal of Hematology (2000 September) 21(9):472-4) describe elevated levels of soluble EPCR in plasma of patients with diseases associated with increased coagulation. This reference is cumulative with the above references in so much as it teaches a correlation in sEPCR with thrombosis and an increased risk of hypercoagulability. Esmon, Thromb. Haemost. (2000 May) 83(5):639-643, is a review article that also discusses the ability of thrombin to increase sEPCR levels (p. 640, end of second to last paragraph). The following two references were published after the effective filing date of the instant application by the inventors and others: Stearns-Kurosawa et al., Hemost. Thromb. Vasc. Biol. (2002 January 15)

99(2):526-530, teach the claimed methods; and, Stearns-Kurosawa et al., J. Thromb. Haemost. (2003 April) 1(4):855-856, teach that a bimodal distrubution of sEPCR is found in certain healthy populations (*e.g.*, those from Italy or France) and suggest that before using sEPCR as an indicator, gender and geographic location should be taken into account in determining what normal levels are. The latter reference suggests that that claimed invention may have inoperative embodiments, but this would be for a minority of the cases.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791 (changing to (571)272-0873 on 01/23/04). Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 9:00AM to 3:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564 (changing to (571)272-0871 on 01/23/04).

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

January 7, 2004